IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	:	Oleg Iliich Epshtein
Title of Invention	:	Method For Correcting Immune Responses And Medical Agent
Date Filed	:	January 22. 2005
Serial No.	:	10/522,651
Examiner	:	Pak, Michael D.
Art Unit	:	1646

DECLARATION UNDER 37 CFR 1.132

I, Oleg I. Epstein, do hereby declare as follows:

1. My name is Dr. Oleg I. Epstein (aka Epshtein). I am a widely recognized scientist in the fields of pharmacology, physiology, and homeopathic technology. I authored well over 100 articles in the peer-reviewed journals.

2. The company I lead, Materia Medica Holding, successfully sells the product covered by the above-identified application 10/522,651. I am the inventor of the '651 application.

3. It is my understanding that the claims of the '651 application stand rejected as allegedly anticipated by U.S. Patent No. 5,698,195 to Le et al. ("*Le*"). In my understanding, the term "anticipate" means *Le* discloses the same invention as claimed in the '651 application, namely, a "homeopathically activated form" of antibodies to TNA-α.

4. I reviewed *Le* in its entirety.

5. It is my opinion as one skilled in the arts of pharmacology and homeopathic technology that *Le* does not disclose a "homeopathically activated" or "homeopathically potentised" form of an antibody. The bases for my opinion are set forth below.

6. "Homeopathic potentization" is a term with well-defined meaning in the art of homeopathy.

7. Attached herewith as Exhibit A is an excerpt from a published English language translation of German Homoeopathic Pharmacopoeia (GHP) (1991). GHP is a voluminous, standard reference text on homeopathy. The attached Exhibit A includes the i) the title page, ii) the content page, iii) a page from the section entitled "Formulations and Presentations," and iv) a portion of the monograph entitled "Manufacture."

8. In the section of the attached Exhibit A entitled Formulations and Presentations, the GHP teaches:

> Liquid formulations are mother tinctures and solutions, as well as liquid dilutions of these; solid formulations are triturations of these (triturations). Different concentrations of these formulations (degrees of dilution) are obtained by *potentization*.
>
> *Potentization* in this context is the dilution by stages of solid or liquid formulations by the stated Method.
>
> The letter x [D in German usage] is used to designate dilutions made in a ratio of 1:10, the letter c [C in German usage] dilutions made in a ratio of 1:100.
>
> A figure added to the designatory letters 'x' and 'c' refers to the number of dilution stages [*emphasis in the original*].

9. In the section entitled "Manufacture," the GHP describes standard homeopathic preparation technologies for various known homeopathic preparations. For each described method, the GHP describes the necessary potentization methodology.

10. Therefore, it is my opinion that the term "homeopathic activation or potentization" has a well defined to one skilled in the art at the time of filing of the '651 application. Attached Exhibit A well informs this meaning.

11. It is my further opinion that no specific process description set forth in *Le* could be expected to lead to homeopathic potentization. For example, while homeopathic potentization can be obtained through various means, the most common form of obtaining potentization is dilution in stages, coupled with external shaking, electromagnetic treatment, etc. None of the processes disclosed in *Le* involve any steps that I as one skilled in the art, would expect will lead to homeopathic potentization.

All statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment; or both, under Section 1001 of Title 18 of the U.S. Code and that such willful false statements may jeopardize the validity of any patent application issuing thereon.

Dated: November 12, 2009

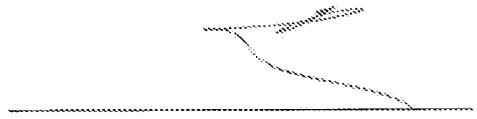

EXHIBIT A

German Homoeopathic Pharmacopoeia (GHP)

(Homöopathisches Arzneibuch)

Translation of the 5 Supplement (1991) to the 1978 edition
OFFICIAL EDITION

Translation sponsored by the
BRITISH HOMOEOPATHIC ASSOCIATION

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Contents

German Homoeopathic Pharmacopoeia, 5th Supplement to 1978 edition

FORMULATIONS AND PRESENTATIONS

Liquid formulations are mother tinctures and solutions, as well as liquid dilutions of these; solid formulations are triturations and solid dilutions of these (triturations). Different concentrations of these formulations (degrees of dilution) are obtained by *potentization*.

Potentization in this context is the dilution by stages of solid or liquid formulations by the stated Method.

The letter x [D in German usage] is used to designate dilutions made in a ratio of 1 : 10, the letter c [C in German usage] dilutions made in a ratio of 1 : 100. The statement 'in a ratio of 1:10' refers to 1 part being processed with 9 parts; correspondingly the statement 'in a ratio of 1:100' refers to 1 part being processed with 99 parts.

A figure added to the designatory letters 'x' and 'c' normally refers to the number of dilution stages.

Liquid dilutions are made in vessels with a capacity of not less than one third greater than the volume of liquid to be used. For potentization, dilute according to the prescribed Method and shake vigorously at least ten times. Use a separate vessel for every dilution (multi-glass method).

If machines are used to shake the dilutions, care must be taken to see that the motions of the machine correspond to those used manually with regard to both frequency and distance moved. Use a separate vessel for every dilution (multi-glass method).

Solid dilutions are made by Method 6 or 7.

Unless otherwise stated, no dilution stage should be omitted when making solid or liquid dilutions.

If the concentration of ethanol used to make a liquid dilutions (ethanol 30% or ethanol 15%) differs from that prescribed in a given case, this must be clearly stated on the label.

Other presentations (tablets, granules, suppositories, eye drops, mixtures, LM potencies, globuli velati, potentized mixtures, nose drops and liquid vinous dilutions) may be produced from liquid and solid formulations.

To put up triturations in capsules as unit doses, use clear hard gelatin capsules that meet the requirements of the Pharmacopoeia.

Unless otherwise stated, formulations and presentations are produced by the Methods given below. The term 'parts' refers to parts by weight unless otherwise stated in the Monograph. Particle sizes are given by the nominal mesh aperture given in μm in parentheses after the name of the substance or the method of reduction in size. Unless otherwise stated in a Monograph, drugs are reduced to the following particle sizes prior to extraction:

leaves, flowers, herbaceous parts	minced	(4000)
wood, bark, roots	minced	(2800)
fruit, seed	minced	(2000)
alkaloid drugs	powdered	(710)

'Water' refers to 'purified water' (German P.), which is used in all manufacturing processes.

All manufacturing processes are carried out in apparatus made from non-

MANUFACTURE

Method 1: Mother tinctures and liquid dilutions
Mother tinctures by Method 1 are mixtures of equal parts of expressed juice and ethanol 86 per cent.

Express the finely cut plants or parts of plants, and immediately mix the expressed fluid with an equal part by weight of ethanol 86 per cent. Leave to stand in a closed container for not less than 5 days at a temperature not exceeding 20 °C; filter.

Adjustment to any parameter given in the Monograph
Determine the dry residue or solid content of the above filtrate. Calculate the amount of ethanol 43 per cent (E_1) required, using Formula (1):

$$E_1 = \frac{W\,(N_x - N_0)}{100}\ [kg] \qquad (1)$$

W = weight of filtrate in kg
N_0 = dry residue or solid content in per cent as required by Monograph
N_x = dry residue or solid content of filtrate in per cent.

Combine the filtrate with the required amount of ethanol 43 per cent. Leave to stand at a temperature not exceeding 20 °C for not less than 5 days; filter if necessary.

Potentization
The 1st decimal dilution (1x) is made with
2 parts of the mother tincture and
8 parts of ethanol 43 per cent,

the 2nd decimal dilution (2x) with
1 part of the 1st decimal dilution and
9 parts of ethanol 43 per cent.
Subsequent dilutions are produced in the same way.

The 1st centesimal dilution (1c) is made with
2 parts of the mother tincture and
98 parts of ethanol 43 per cent,

the 2nd centesimal dilution (2c) with
1 part of the 1 st centesimal dilution and
99 parts of ethanol 43 per cent.
Subsequent dilutions are produced in the same way.

Method 2a: Mother tinctures and liquid dilutions
Mother tinctures manufactured by Method 2a are produced by macerating the

material as described below (ethanol content approx. 43 per cent).

The plants or parts of plants are finely minced. A sample is used to determine loss on drying. To the minced plant material add immediately not less than half the amount by weight of ethanol 86 per cent and store in well sealed containers at a temperature not exceeding 20 °C.

Calculate the amount of ethanol 86 per cent required (E_2), for the plant material, using Formula (2), deduct the amount of ethanol that has already been used, and add the final amount to the mixture.

$$E_2 = \frac{M \cdot D}{100} \text{ [kg]} \qquad (2)$$

M = weight of plant material in kg
D = loss on drying in sample, in per cent.

Leave the mixture to stand for not less than 10 days at a temperature not exceeding 20 °C, shaking repeatedly. Express and filter.

Adjust to any parameters given in the Monograph, as for Method 1.

Potentize as shown under Method 1.

Method 2b: Mother tinctures and liquid dilutions

Mother tinctures made in accordance with Method 2b are manufactured as per Method 2a, using ethanol 62 per cent (ethanol content approx. 30 per cent).

Use ethanol 30 per cent to adjust to any concentration required in the Monograph.

Potentization

The 1st decimal dilution (1x) is made with
2 parts of the mother tincture and
8 parts of ethanol 30 per cent,

the 2nd decimal dilution (2x) with
1 part of the 1st decimal dilution and
9 parts of ethanol 15 per cent.

Subsequent dilutions are produced in the same way.

Method 3a: Mother tinctures and liquid dilutions

Mother tinctures for Method 3a are produced according to Method 2a (ethanol content approx. 60 per cent), with the following difference: The required amount of ethanol 86 per cent (E_3), is calculated according to Formula (3).

$$E_3 = \frac{2 \cdot M \cdot D}{100} \text{ [kg]} \qquad (3)$$

M = weight of plant material in kg
D = loss on drying in sample, in per cent.

Use ethanol 62 per cent to adjust to any concentration required as per Monograph.

Potentization

The 1st decimal dilution (1x) is made with
3 parts of the mother tincture and
7 parts of ethanol 62 per cent,

the 2nd decimal dilution (2x) with
1 part of the 1st decimal dilution and
9 parts of ethanol 62 per cent.

Subsequent dilutions are produced in the same way. For dilutions from the 4th decimal onwards use ethanol 43 per cent.

The 1st centesimal dilution (1c) is made with
3 parts of the mother tincture and
97 parts of ethanol 62 per cent,

the 2nd centesimal dilution (2c) with
1 part of the 1st centesimal dilution and
99 parts of ethanol 43 per cent.

Subsequent dilutions are produced in the same way.

Method 3b: Mother tinctures and liquid dilutions

Mother tinctures for Method 3b are produced according to Method 3a, using ethanol 73 per cent (ethanol content approx. 43 per cent).

Use ethanol 43 per cent to adjust to any concentration required in the Monograph.

Potentization

The 1st decimal dilution (1x) is made with
3 parts of the mother tincture and
7 parts of ethanol 43 per cent,

the 2nd decimal dilution (2x) with
1 part of the 1st decimal dilution and
9 parts of ethanol 30 per cent,

the 3rd decimal dilution (3x) with
1 part of the 2nd decimal dilution and
9 parts of ethanol 15 per cent.

Subsequent dilutions are produced in the same way.

Method 3c: Mother tinctures and liquid dilutions

Mother tinctures for Method 3c are produced according to Method 3a using, ethanol 43 per cent (ethanol content approx. 30 per cent).

Use ethanol 30 per cent to adjust to any concentration required in the Monograph.

Potentization
The 1st decimal dilution (1x) is made with
3 parts of the mother tincture and
7 parts of ethanol 30 per cent,

the 2nd decimal dilution (2x) with
1 part of the 1st decimal dilution and
9 parts of ethanol 15 per cent.
Subsequent dilutions are produced in the same way.

Method 4a: Mother tinctures and liquid dilutions
Method 4a is for mother tinctures manufactured according to the maceration or percolation methods described in the TINKTUREN (tinctures) Monograph in the German Pharmacopoeia using 1 part of the drug to 10 parts of ethanol in suitable concentration (unless otherwise stated in the Monograph). If adjustment to a given value is necessary, the required amount of ethanol in the concentration prescribed or used for manufacture is calculated according to Formula (1). The calculated amount of ethanol is combined with the filtrate. The mixture is left to stand for not less than five days at a temperature not exceeding 20 °C, after which it is filtered if required.

Potentization
The mother tincture is equivalent to the 1st decimal dilution (ø = 1x).

The 2nd decimal dilution (2x) is made with
1 part of the mother tincture and
9 parts of ethanol of the same concentration.

the 3rd decimal dilution (3x) with
1 part of the 2nd decimal dilution and
9 parts of ethanol of the same concentration.
Ethanol 43 per cent is used for subsequent dilutions from the 4th decimal upwards unless a different concentration is prescribed; the method is the same as for the 3rd decimal dilution.

The 1st centesimal dilution (1c) is made with
10 parts of the mother tincture and
90 parts of ethanol of the same concentration.

the 2nd centesimal dilution (2c) with
1 part of the 1st centesimal dilution and
99 parts of ethanol 43 per cent, unless another concentration is prescribed.
Subsequent dilutions are produced in the same way.

Method 4b: Mother tinctures and liquid dilutions
Method 4b is for mother tinctures manufactured according to the maceration or

percolation methods described in the TINKTUREN (tinctures) Monograph in the German Pharmacopoeia using 1 part of animals, parts of animals or animal secretions and 10 parts of ethanol in suitable concentration. If adjustment to a given value is necessary, the required amount of ethanol in the concentration prescribed or used for manufacture is calculated according to Formula (1). The calculated amount of ethanol is combined with the filtrate. The mixture is left to stand for not less than five days at a temperature not exceeding 20 °C, after which it is filtered if required.

Potentization
The mother tincture is equivalent to the 1st decimal dilution (ø = 1x).

The 2nd decimal dilution (2x) is made with
1 part of the mother tincture and
9 parts of ethanol of the same concentration.

the 3rd decimal dilution (3x) with
1 part of the 2nd decimal dilution and
9 parts of ethanol of the same concentration.
Ethanol 43 per cent is used for subsequent dilutions from the 4th decimal upwards; the method is the same as for the 3rd decimal dilution.

The 1st centesimal dilution (1c) is made with
10 parts of the mother tincture and
90 parts of ethanol of the same concentration.

the 2nd centesimal dilution (2c) with
1 part of the 1st centesimal dilution and
99 parts of ethanol 43 per cent.
Subsequent dilutions are produced in the same way.

Method 5a: Solutions
Liquid preparations made by Method 5a are solutions produced from basic drug materials and a liquid vehicle. Unless otherwise prescribed in the Monograph, 1 part of the basic drug material is dissolved in 9 parts (= 1x) or 99 parts (= 1c or 2x) of the liquid vehicle and succussed. Absolute ethanol, purified water, glycerol 85 per cent and the ethanol/water mixtures listed in the GHP are used as vehicles.

If ethanol 15 per cent is the prescribed vehicle for the liquid preparation, the solution may also be produced by the following method: 1 part of the basic drug material is dissolved in 7.58 parts of water, to produce the 1x; add 1.42 parts of ethanol to the solution. To produce the 1c or 2x, 1 part of the basic drug material is dissolved in 83.4 parts of water, adding 15.6 parts of ethanol to the solution.

Potentization
The 2nd decimal dilution (2x) is made with
1 part of the mother tincture and
9 parts of ethanol 43 per cent,

unless another vehicle is prescribed. Subsequent dilutions are produced in the same way.

The 2nd centesimal dilution (2c) is made with
1 part of the 1st centesimal dilution (1c) and
99 parts of ethanol 43 per cent,
unless another liquid vehicle is prescribed. Subsequent dilutions are produced in the same way.

Method 5b: Aqueous solutions
Liquid preparations made by Method 5b are solutions produced from basic drug materials and WATER FOR INJECTIONS. Unless otherwise stated in the Monograph, 1 part of the basic drug material is dissolved in 9 parts (= 1x) or 99 parts (= 1c or 2x) of WATER FOR INJECTIONS and succussed.

Potentization
The 2nd decimal dilution (2x) is made with
1 part of the solution (1x) and
9 parts of WATER FOR INJECTIONS.
Subsequent dilutions are produced in the same way.

Aqueous solutions produced by Method 5b are normally processed immediately; their use is limited to the manufacture of preparations by Methods 11, 13, 14, 15, 39a and 39c.

Solutions made according to Method 5b and their liquid dilutions must comply with the 'Sterility Test' given in the German Pharmacopoeia if stored.

LABELLING
Preparations made according to Method 5b carry the designation 'aquos.' after the indication of the potency; the same applies to presentations made from them.

Method 6: Triturations
Preparations made according to Method 6 are triturations of solid basic drug materials with lactose as the vehicle unless otherwise prescribed. Triturations up to and including the 4th dilution are triturated by hand or machine in a ratio of 1 to 10 (decimal dilution) or 1 to 100 (centesimal dilution). Unless otherwise stated, the basic drug materials are reduced to the particle size given in the Monograph (mesh aperture). Quantities of more than 1,000 g are triturated by mechanical means.

The duration and intensity of trituration should be such that the resulting particle size of the basic drug material in the 1st decimal or centesimal dilution is below 10 μm at 80 per cent level; no drug particle should be more than 50 μm.

Triturations up to and including the 4th decimal or centesimal are produced at the same duration and intensity of trituration.

Trituration by hand
Divide the vehicle into three parts and triturate the first part for a short period in a porcelain mortar. Add the basic drug material and triturate for 6 minutes, scrape

down for 4 minutes with a porcelain spatula, triturate for a further 6 minutes, scrape down again for 4 minutes, add the second part of the vehicle and continue as above. Finally add the third part and proceed as before. The minimum time required for the whole process will thus be 1 hour. The same method is followed for subsequent dilutions.

For triturations above the 4x or 4c dilute 1 part of the dilution with 9 parts of lactose or 99 parts of lactose as follows: in a mortar, combine one third of the required amount of lactose with the whole of the previous dilution and mix until homogeneous. Add the second third of the lactose, mix until homogeneous, and repeat for the last third.

Trituration by machine

Up to and including the 4th dilution, triturations are made in a machine fitted with a scraping device that ensures even trituration.

Other machines may be used, providing the particle sizes produced meet requirements.

To produce a trituration by machine, triturate one third of the vehicle, add the basic drug material and triturate; finally add the remaining vehicle in two equal portions and triturate. The time required to produce one trituration by machine is not less than 1 hour.

Dilutions above the 4x or 4c are made by diluting 1 part of the dilution with 9 parts of lactose or 99 parts of lactose and combining one third of the required amount of lactose in a suitable mixer with the whole of the previous dilution and mixing until homogeneous. Add the second third of the lactose, mix until homogeneous, and proceed in the same way with the last third of the lactose.

The choice of a suitable mixer and the mixing time required to achieve homogeneity are established in a single trial run for each type of apparatus and recorded. Additional requirements relating to the machine in question are determined, recorded and written down in the operating instructions for the production process.

Method 7: Triturations

Preparations made by Method 7 are solid preparations of mother tinctures and solutions and their dilutions with lactose as the vehicle.

The total amount of lactose required is transferred to a suitable apparatus, and the prescribed amount of the liquid preparation in the previous dilution stage is gradually mixed in. The moist homogeneous mix is dried with care, ground if necessary and sieved before mixing again thoroughly.

The amount of lactose used should be such that the preparation will have the prescribed total weight when the manufacturing process is complete.

Quantities of more than 1,000 g are made by mechanical trituration; the type of mixer, mixing period, drying time and length of the final mixing stage are determined in a single trial run, recorded and written down in the operating instructions for the production process.

Potentization

Mother tinctures, solutions and liquid dilutions are potentized in the relative

quantities laid down for their production. Lactose serves as the vehicle; the amount of lactose added must be such that the total weight is 10 parts for decimal and 100 parts for centesimal potencies.

Method 8a: Liquid preparations made from triturations
Preparations made by Method 8a are liquid preparations produced from triturations made by Method 6.

To produce a 6x liquid dilution, 1 part of the 4x trituration is dissolved in 9 parts of water and succussed. 1 part of this dilution is combined with 9 parts of ethanol 30 per cent to produce the 6x liquid dilution by succussion. In the same way, the 7x liquid dilution is made from the 5x trituration, and the 8x liquid dilution from the 6x trituration. From the 9x upwards, liquid decimal dilutions are made from the previous decimal dilution with ethanol 43 per cent in a ratio of 1 to 10.

To produce a 6c liquid dilution, 1 part of the 4c trituration is dissolved in 99 parts of water and succussed. 1 part of this dilution is combined with 99 parts of ethanol 30 per cent to produce the 6c liquid dilution by succussion. In the same way, the 7c liquid dilution is made from the 5c trituration, and the 8c liquid dilution from the 6c trituration. From the 9c upwards, liquid centesimal dilutions are made from the previous centesimal dilution with ethanol 43 per cent in a ratio of 1 to 100.

The 6x, 7x, 6c and 7c liquid dilutions produced by the above method must not be used to produce further liquid dilutions.

Method 8b: Aqueous preparations made from triturations
Preparations made by Method 8b are aqueous preparations produced from triturations made by Method 6.

To produce a 6x liquid dilution, 1 part of the 4x trituration is dissolved in 9 parts of WATER FOR INJECTIONS and succussed. 1 part of this dilution is combined with 9 parts of WATER FOR INJECTIONS to produce the 6x liquid dilution by succussion. In the same way, the 7x liquid dilution is made from the 5x trituration, and the 8x liquid dilution from the 6x trituration. From the 9x upwards, liquid decimal dilutions are made from the previous decimal dilution with WATER FOR INJECTIONS in a ratio of 1 to 10.

6x and 7x liquid dilutions made by the above method must not be used to produce further liquid dilutions.

Aqueous preparations made by Method 8b are normally processed immediately; their use is limited to the manufacture of presentations by Methods 11, 13, 14, 15, 39a and 39c, mixtures by Method 16, and potentized mixtures by Method 40b.

Aqueous preparations made by Method 8b must comply with the 'Sterility Test' of the German Pharmacopoeia if stored.

LABELLING
Preparations made by Method 8b carry the designation 'aquos.' after the indication of the potency; the same applies to presentations made from them.

Method 9: Tablets
Tablets made by Method 9 are produced from preparations made by Method 6 or